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A PLASMA-GENERATED COATING APPARATUS FOR MEDICAL DEVICES AND A METHOD OF COATING DEPOSITION

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BACKGROUND

1. Field of the Invention

This invention relates to an apparatus for fabricating plasma-generated coatings for medical devices such as stents. The invention also relates to method of coating such devices.

2. Background

Stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Stents are usually compressible, so that they can be inserted through small cavities via catheters, and then expanded to a larger diameter once they are at the desired location. FIG. 1 illustrates one example of a conventional vascular stent 10. The stent 10 includes struts 12 connected by elements 14. The combination of the struts 12 and the elements 14 define a tubular body of the stent 12. The tubular body has an outer surface 16 and an inner surface 18. Although the rate of restenosis has been reduced by mechanical intervention of stents, restenosis still presents a significant medical problem. Accordingly, stents have been modified to function not only as mechanical scaffolding, but also to provide biological therapy.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

One conventional method of medicating a stent involves the use of a polymeric carrier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent. The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the therapeutic substance impregnated in the polymer.

One of the drawbacks and disadvantages associated with the use of medicated stents has been the aggregation of platelets on the device. A high degree of such aggregation, combined with the early onset of monocyte activation, is believed to be a factor leading to restenosis. One way to reduce platelet aggregation, as well as the early onset of monocyte activation, is believed to be by forming the stent coating using the process of plasma polymerization. Plasma polymerization, also known as glow discharge polymerization, is a method of polymerizing organic substances from vapor phase at low pressures. Plasma polymerization is generally performed by introducing a gas including one or more monomers into a vacuum zone in which the substrate to be coated is placed. The polymerizable monomers are then subjected to an electric discharge to generate ions and/or free radicals. While plasma polymerization can

produce coatings having good properties, improvements in the quality of the coatings is desired. For instance, due to the harsh conditions existing in the plasma environment, some areas of the plasma-formed stent coatings can include defects such as burn marks, excessive roughness, and sometimes even delamination. It is desirable to eliminate or at least minimize these problems. Additionally, existing plasma polymerization technologies allow coating of only one stent at a time. To increase production of drug eluting stents, it is desirable to be able to form a plasma polymerized coating on many stents simultaneously. The embodiments of the present invention address these and other issues associated with coating of implantable medical devices.

SUMMARY

An apparatus to plasma coat a stent, is disclosed, comprising a mandrel supporting a stent; a first plasma member circumscribing the mandrel, the first plasma member being grounded; a second plasma member circumscribing the first plasma member; and a plasma generating source in communication with the second plasma member. In one embodiment, the first plasma member is a first hollow tubular body in which the mandrel is positioned, and the second plasma member is a second hollow tubular body in which the first hollow tubular body is positioned. The first and second hollow tubular bodies can include perforations or have a screen or mesh-like body. In accordance with another embodiment, the first plasma member is a hollow tubular body in which the mandrel is positioned and the second plasma member is a coil element wrapped around the first tubular body. The plasma generating source can be a radio frequency generating source or a microwave generating source. The apparatus can also include a first plate member in communication with the first plasma member; a second plate member positioned over the first plate member and in commutation with the second plasma member; and an insulator disposed between the first and second plate members to electrically insulate the plate members. The mandrel can extend from the first plate member into the first plasma element.

An apparatus to coat an implantable medical device, is provided comprising a first tubular member; a second tubular member in which an implantable medical device can be placed, the second tubular member being positioned within the first tubular member and the second tubular member being electrically isolated from the first tubular member; and an energy source in communication with the first tubular member. The tubular members can include bodies having holes disposed therein. The energy source can be configured to create

plasma within the first tubular body. The second tubular body can be coupled to a ground source.

A method of forming a coating for an implantable medical device is also provided using the aforementioned devices.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a conventional stent.

FIG. 2 is a schematic view of a plasma polymerization apparatus for housing implantable medical devices during polymerization process.

FIG. 3 is a perspective view of the plasma polymerization apparatus in accordance with one embodiment of the invention.

FIG. 4 is a top view of the apparatus of FIG. 3.

FIG. 5 is a side view of a plasma polymerization apparatus according to another embodiment of the invention.

FIG. 6 is a top view of the apparatus of FIG. 5.

FIGs. 7-10 are microphotographs of various areas of a stent coating made according to an embodiment of the present invention.

FIG. 11 is a microphotograph of a control stent coating.

DETAILED DESCRIPTION

Apparatus

FIGs. 2-6 illustrate a plasma polymerization apparatus 20, in accordance with embodiments of the invention, that can be placed within a pressure controlled plasma chamber 22. The apparatus 20 can be spherical in design and can include an upper plate member 24, a middle plate member 26 and a lower plate member 28. The plate members 24, 26 and 28 can have a general diameter of about 5 to about 6 inches (about 127 mm to 152 mm) and can each have a thickness of about 0.25 about 0.5 inch (about 6 mm to 12 mm). The plate members 24, 26, and 28 can be made of any suitable conductive material such as stainless steel or aluminum. Each member 24, 26, and 28 can be made of the same material or different materials.

The middle plate member 26 and the lower plate members 28 are positioned in close proximity to one another. The distance between the middle plate member 26 and the lower plate 28 can be, for example, about 0.125 to about 0.375 inch (about 3 to 9 mm). The total height of the apparatus 20, measured as the distance between the upper surface of the plate member 24 and the lower surface of the plate member 28, can be between about 3 to 6 inches (about 75 to 150 mm). The plate members 26 and 28 are separated by insulating material 30, such a ceramic material, an example of which can be alumina (Al_2O_3). The lower plate member 30 can be grounded.

A plurality of plasma regions or cavities 32 are disposed between the upper plate member 24 and the middle plate member 26. Referring to FIGs. 3 and 4, the plasma cavities 32 are defined by the space created within first plasma elements or outer screens 34. The outer screens 34 can be made of a metal, such as stainless steel, or alternatively, titanium or aluminum. The outer screens 34 can be made of solid metal tubular sheets, but preferably are mesh-like or

perforated as shown by FIGs. 3 and 4. It its believed that perforation of the screens 34 provides a plasma generated coating with better uniformity and better physical and mechanical properties. The total area covered by perforation can be about 64 % of the surface of the screen 34. The diameter of the perforations can be from about 0.25 to about 0.375 inch (about 3 to 9 mm), for example about 0.3 inch (about 7.5 mm). The inner diameter of each of the screens 34 is between about 1 to 2 inches (about 25 to 50 mm). As illustrated by FIGs. 3 and 4, the upper plate member 24 can include circular openings 36 at the top of each of the tubular screens 34. As best illustrated by the figures, the middle plate member 26 includes respective openings for allowing mandrels 38, for supporting the stents, to extend from the lower plate 28 into the plasma cavities 32.

As illustrated in Figure 4, second plasma elements or inner screens 40, similar to that of the outer screens 34 but of smaller diameter, are positioned within the outer screens 34. The inner screens 40 and the outer screens 34 are positioned concentrically; however, a slight (~5-10%) deviation from the concentricity is acceptable, although not preferred. The inner screens 40 are also made of a metal, such as stainless steel, or alternatively, titanium or aluminum. The inner screens 40 can also be made of a solid tubular metal sheet, but preferably are perforated or mesh-like as well. Perforations allow a better access of radicals and ions generated by plasma to the central area of cavities 32. The total area covered by perforation can be about 64 % of the surface of the inner screen 40. The diameter of the inner screen 40 can be about 0.5 to 1 inch (about 12.5 to 25 mm).

The upper and middle plates 24 and 26 and the outer screens 34 are in electric communication with one another as to form an electric circuit. To generate plasma, a radio-frequency (RF) signal can be directed to the upper 24 or middle plate 26. By way of example, a

radio frequency source such as Cesar 133, 300W unit, manufactured by Dressler of Germany can be used. Alternatively, instead of using the RF signal, plasma-can be generated using a microwave source, or any other suitable source known to those having ordinary skill in the art.

It is desirable that the plasma exist only within the space defined by cavities 32 but not outside this space. It is also desirable to avoid arcing to the stent surface and eliminate dielectric break down of the substrate film. In order to insure that the plasma will exist only within the space defined by cavities 32 (which includes the space inside the inner screens 40), as well as to avoid arcing to the stent surface and eliminate dielectric break down of the substrate film, the inner screens 40 are grounded by being in communication with the bottom plate 28. The inner screen 40 and the mandrel 38 are not seen in the central cavity of the apparatus shown by FIG. 4, but in fact the inner screen 40 and the mandrel 38 can also be used in this central cavity. The inner screen 40 and the mandrel 38for the central cavity are provided on the chamber 22, and the inner screen 40 and mandrel 38 are inserted in the central cavity when the apparatus of FIG. 4 is placed in the chamber 22.

The mandrels 38, for supporting stents, extend from the lower plate 28 through the openings of the middle plate 26 and into the plasma cavities 32. The mandrels 38 do not make contact with the middle plate 26. For better quality and uniformity of the coating, the mandrels 38 and the stents are preferably positioned in the center of the cavities 32 (i.e., in the center of inner as well as outer screens 34 and 40); however, positioning the mandrels 38 and the stents between about 5 to 10 % off center is acceptable, but not preferred. The mandrels 38 should support the stents without the stents contacting the inner screen 40. The mandrels are made of stainless steel and are also grounded.

In accordance to another embodiment, as illustrated by FIGs. 5 and 6, in lieu of perforated outer screens 34, coils 42 wrapped around the grounded inner tubular perforated screens 40, can be used to generate the plasma. The coils 42 can be coupled to the upper 24 or middle 26 plate member. The coils 42 can be wrapped around the inner screens 40 any suitable number of times (e.g., 4 to 8) and can include an inner spatial diameter of about 1 to 2 inches (about 25 to 50 mm). The coils 42 can be made from stainless steel and can have a coil diameter of about 1.5 to 2 inches (about 37 to 50 mm).

Method of Coating

Any portion of the outer surface 16 of the stent 10 can be modified using gaseous plasma according to embodiments of the present invention. The surface modification includes formation of a polymer film on the surface 16 of the stent 10, the polymer film formed as a result of the process of plasma-induced polymerization of monomer(s), oligomer(s), or prepolymer(s). A polymerizable monomer gas can be introduced into the plasma chamber, and the RF field can be applied to induce polymerization of the monomer on the surface 16 of the stent 10 to form the polymer film, i.e., a "plasma-polymerized film." The surface modification is not intended to be limited to any particular region of the outer surface 16 of the stent 10.

Examples of polymerizable monomeric gases that can be used to deposit a plasma-polymerized film on the surface 16 of the stent 10 include fluorinated compounds such as fluorinated alkanes, fluorinated alkenes, and their derivatives, for example, vinylidene fluoride (VDF), 1,2-difluoroethane, tetrafluoroethylene, or hexafluoropropene (HFP), or mixtures thereof.

In addition, some non-fluorinated compounds, such as alkenes, (meth)acrylates, and glycol-like monomers (glymes) can be used. Some examples of suitable (meth)acrylates include acrylic acid (AA), butyl methacrylate (BMA), or 2-hydroxyethyl methacrylate (HEMA). With

AA, carbon dioxide can also be added to the feed mixture introduced into the chamber 22. Examples of alkenes include ethylene or propylene. Examples of glycol-like monomers include diglyme, triglyme or ethylene oxide.

If VDF is used to form a polymer on the surface 16 of the stent 10, it is known that under plasma conditions, a multi-step process occurs, whereby VDF having the formula $CH_2=CF_2$ fragments into methylene radicals ($:CH_2$) and difluoromethylene radicals ($:CF_2$) along with various other decomposition products such as ($:CH\cdot$) and ($H\cdot$), followed by the recombination thereof. Among possible paths of such recombination is a reaction between only the methylene radical species (reaction I) or a reaction between one methylene radical and one difluoromethylene radical species (reaction II):

$$(n/2):CH_2 + (n/2):CH_2 \rightarrow -[CH_2–CH_2]_n– \quad (I)$$

$$(m/2):CH_2 + (m/2):CF_2 \rightarrow -[CH_2–CF_2]_m–, \quad (II)$$

where "n" and "m" are integers. Another possible path can lead to recombination of difluoromethylene radicals to form some amount of poly(vinylidene fluoride)(PVDF) on the stent surface.

The process of polymerization predominantly follows reaction path (I) at lower pressures (less than about 30 mTorr, for instance, about 20 mTorr) leading to formation of mostly poly(ethylene)-like polymer on the surface 16 of the stent 10. At higher pressures (above about 80 mTorr, for example, about 90 mTorr), due to the formation of difluoromethylene radical species, reaction (II) predominantly occurs, where recombination takes place equally between fluorinated and protonated methylene species. As a result, at higher pressures (>60mTorr) mostly a poly(vinylidenefluoride)(PVDF)-like polymer is obtained.

VDF can be introduced into the plasma chamber at a flow rate of about 45-60 sccm, followed by introduction of argon into the plasma chamber. Argon plasma can be then initiated by applying the RF power of about 60 W to cause the formation of the polymer coating on the surface 16 of the stent 10. The time needed for plasma-induced polymerization can be between about 2 to 15 minutes. The plasma is then turned off by terminating the RF power.

If acrylic acid (AA) is used to form a polymer on the surface 16 of the stent 10, the parameters which can be used to conduct the process of plasma-induced polymerization are reflected in Table 1.

Table 1

Process Parameters	Parameter Range	Exemplary Value
carbon dioxide flow rate (sccm)	60 to 200	90
acrylic acid flow rate (ml/min)	0.05 to 0.35	0.2
pressure (mTorr)	70 to 250	150
RF power (W)	50 to 250	100
RF frequency (MHz)	2 to 2800	13.54
power/flow rate (MJ/Kg)	9 to 35	13.7

The thickness of the plasma-polymerized film formed on the surface 16 of the stent 10 formed from AA can be between about 20 nm and about 500 nm, for example, between about 70 nm and about 150 nm, such as about 125 nm. The duration of the process of applying the acrylic acid plasma depends on the thickness of the polymer film that is desired to be achieved on the surface 16 of the stent 10. For example, the AA plasma can be applied for about 10

minutes. As indicated by Table 1, carbon dioxide can be also optionally provided with the stream of AA, if it is desirable to limit the rate of de-carboxylation which can occur with an organic acid in a plasma field.

A pulsed plasma, known to those having ordinary skill in the art, can be optionally used for plasma polymerization of AA. If the pulsed plasma is utilized, the process parameters are similar to those of Table 1, except the power range can be between about 80 Watts and about 450 Watts, for example, between about 250 Watts and about 350 Watts. With the pulsed plasma embodiment, the RF power can be pulsed at between about 500 Hz and about 4 kHz, for example, between about 1kHz and about 1.25 kHz using, for example, a square wave pulse sequence. The duty period (i.e., the time in which the power is on) can be between about 15% and about 100%, for example, between about 20% and about 35%. With the use of pulsed plasma condition, the rate of de-carboxylation can be further limited.

Following deposition of the plasma-polymerized film on the surface 16 of the stent 10, the plasma field can be purged (quenched) with argon without an applied RF field to allow surface free radicals to recombine prior to exposure to atmospheric oxygen. Table 2 provides parameters for the quenching process:

Table 2

Process Parameter	Parameter Range	Exemplary Value
argon	_	(> 99.9% by volume)
gas flow rate (sccm)	30 to 300	230
Pressure (mTorr)	50 to 500	250
time (minutes)	2 to 10	3

Plasma-induced polymerization using AA yields carboxylated polymers on the surface 16 of the stent 10. The carboxyl groups can be used for the optional conjugating of biocompatible or non-fouling components such as polyethylene glycol, heparin, heparin having hydrophobic counter ions, and superoxide dismutase mimic (SODm).

Optionally, the stent coating can include a region having a drug or therapeutic substance incorporated therein. To form the region having the drug, a polymeric coating impregnated with the drug can be deposited over the plasma-polymerized film. Alternatively, or in addition to being deposed over the plasma-polymerized film, a drug coating can be deposited on the stent and the plasma-polymerized film deposited over the drug coating. To from the drug coating, a polymer can be combined with a therapeutic substance and can be dissolved in a solvent. The solution can be applied onto the stent by any common method, such as spraying or dipping, before and/or after the plasma-polymerized film has been formed. Alternatively, a polymer-free region including the therapeutic substance can be formed, for example, by dissolving the therapeutic substance in a solvent followed by spraying the solution or by dipping the stent in the solution.

Examples of drugs or therapeutic substances that can be used include substances which can inhibit the activity of vascular smooth muscle cells. More specifically, the substance can be aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells for the inhibition of restenosis. The substance can also include any substance capable of exerting a therapeutic or prophylactic effect for the patient. For example, the substance can be for enhancing wound healing in a vascular site or improving the structural and elastic properties of the vascular site. Examples of therapeutic substances include antiproliferative substances such as derivatives and analogs of actinomycin D (manufactured by Sigma-Aldrich of

Milwaukee, Wisconsin), or COSMEGEN available from Merck & Co. Inc. of Whitehouse Station, New Jersey. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The therapeutic substance can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL® by Bristol-Myers Squibb Co. of Stamford, Connecticut), docetaxel (e.g. Taxotere®, from Aventis S.A. of Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, of Peapack New Jersey), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co. of Stamford). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, heparin derivatives having hydrophobic counter ions, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax made by Biogen, Inc., of Cambridge, Massachusetts). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co. of Stamford), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc. of Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., of Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived

Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin; tacrolimus and dexamethasone.

Embodiments of the present invention have been disclosed with reference to a stent, such as balloon expandable or self-expandable stents. However, other implantable medical devices are also within the scope of the invention. Examples of such implantable devices include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, abdominal aortic aneurysm devices, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

The features and advantages of the invention can be further illustrated by the following Example.

Example

Plasma-induced polymerization of a blend of vinylidene fluoride (VDF) and hexafluoropropene (HFP) was conducted using the assembly shown by FIG. 2, where the plasma apparatus shown in FIGs. 5 and 6 was utilized. A 13 mm VISION stent (available from Guidant Corp.) was coated. The conditions of the plasma polymerization process were as shown in Table 3.

Table 3

Process Parameters	Parameter Value
VDF flow rate (sccm)	45
HFP flow rate (sccm)	45
Pressure (mTorr)	90
RF power (W)	80
RF frequency (kHz)	3.5
Duty cycle, %	25
Time, min	5

The process of plasma polymerization took about 5 minutes. After the 5 minutes, the plasma was then turned off by terminating the RF power. Microphotographs of the various areas of the stent coating were then made (FIGs. 7-10).

A control stent was coated using the same VDF-HFP blend, under the same conditions as those described in Table 3. However, to coat the control stent, another apparatus was used instead of the apparatus of the present invention. The control apparatus was similar to the apparatus shown by FIGs. 5 and 6, except that in the control apparatus the inner tubular screen 40 was not grounded. Microphotograph of the control stent coating was then made (FIG. 11).

By comparing the microphotographs shown by FIGs. 7-10 and by FIG. 11, one can see that the process carried in the apparatus of the present invention leads to much better quality of the stent coating. The coating obtained by the apparatus of the present invention was smooth, uniform and did not have any burn marks. By comparison, the control coating has visible defects.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.